

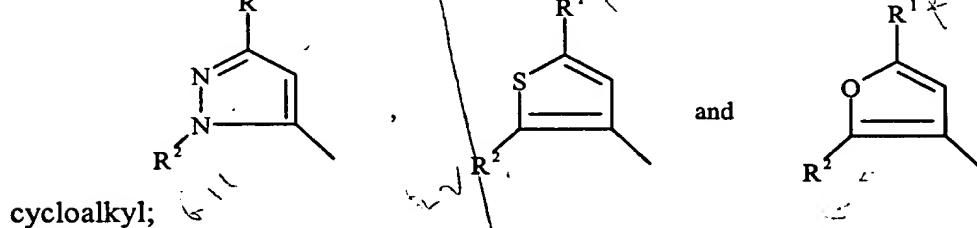
WHAT IS CLAIMED IS:

- Sub A*
1. A method for the treatment of disease other than cancer mediated by



p38 which comprises administering a compound of formula I or a pharmaceutically acceptable salt thereof

- 10 wherein A is a heteroaryl selected from the group consisting of
wherein R¹ is selected from the group consisting of C₃-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₁-C₁₀ alkyl and up to per-halosubstituted C₃-C₁₀



- any?*
- 15 B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

- 20 wherein n is 0-3 and each X is independently selected from the group consisting of -CN, CO₂R⁵, -C(O)NR⁵R⁵, -C(O)R⁵, -NO₂, -OR⁵, -SR⁵, -NR⁵R⁵,

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- NR⁵C(O)OR^{5'}, -NR⁵C(O)R^{5'}, C₁-C₁₀ alkyl, C₂-₁₀-alkenyl, C₁-₁₀-alkoxy, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₇-C₂₄ alkaryl, C₃-C₁₃ heteroaryl, C₄-C₂₃ alkheteroaryl, substituted C₁-C₁₀ alkyl, substituted C₂-₁₀-alkenyl, substituted C₁-₁₀-alkoxy, substituted C₃-C₁₀ cycloalkyl, substituted C₄-C₂₃ alkheteroaryl and -Y-Ar;

- 5 where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)R⁵, -C(O)NR⁵R^{5'}, -OR⁵, -SR⁵, -NR⁵R^{5'}, -NO₂, -NR⁵C(O)R^{5'}, -NR⁵C(O)OR^{5'} and halogen up to per-halosubstitution;

- 10 wherein R⁵ and R^{5'} are independently selected from H, C₁-C₁₀ alkyl, C₂-₁₀-alkenyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, up to per-halosubstituted C₁-C₁₀ alkyl, up to per-halosubstituted C₂-₁₀-alkenyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₆-C₁₄ aryl and up to per-halosubstituted C₃-C₁₃ heteroaryl,

- 15 wherein Y is -O-, -S-, -N(R⁵)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -NR⁵C(O)NR⁵R^{5'}-, -NR⁵C(O)-, -C(O)NR⁵-, -(CH₂)_mS-, -(CH₂)_mN(R⁵)-, -O(CH₂)_m-, -CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁵)(CH₂)_m-,
m = 1-3, and X^a is halogen; and

- 20 Ar is a 5-10 member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)NR⁵R^{5'}, -C(O)NR⁵, -NO₂, -OR⁵, -SR⁵, -NR⁵R^{5'}, -NR⁵C(O)OR^{5'}, -OC(O)R⁵, -NR⁵C(O)R^{5'}, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, substituted C₁-C₁₀ alkyl, substituted C₃-C₁₀ cycloalkyl, substituted C₇-C₂₄ alkaryl and substituted C₄-C₂₃ alkheteroaryl;

25 wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)NR⁵R^{5'}, -OR⁵, -SR⁵, -NO₂, -NR⁵R^{5'}, -NR⁵C(O)R^{5'} and -NR⁵C(O)OR^{5'}, and

- 30 wherein R² is C₆-C₁₄ aryl, C₃-C₁₄ heteroaryl, substituted C₆-C₁₄ aryl or substituted C₃-C₁₄ heteroaryl,

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wherein if R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n ,

wherein $n = 0-3$ and each V is independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)NR^5R^5'$, $-OR^5$, $-SR^5$, $-NR^5R^5'$, $-C(O)R^5$,
5 $-OC(O)NR^5R^5'$, $-NR^5C(O)OR^5'$, $-SO_2R^5$, $-SOR^5$, $-NR^5C(O)R^5'$, $-NO_2$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alk heteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alk heteroaryl,
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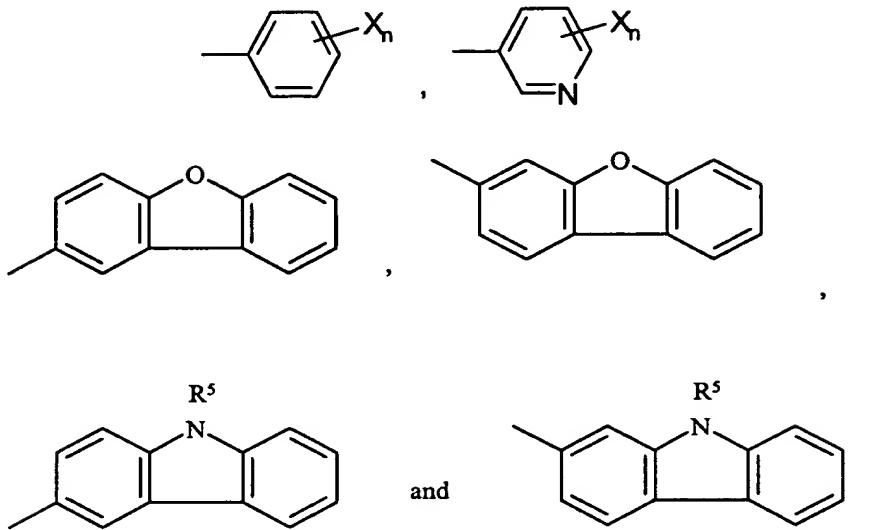
where V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^5'$, $-NR^5R^5'$, $-OR^5$, $-SR^5$,
- $NR^5C(O)R^5'$, $-NR^5C(O)OR^5'$ and $-NO_2$,

15 wherein R^5 and R^5' are each independently as defined above.

2. A method as in claim 1, wherein R^2 is selected from substituted or unsubstituted members of the group consisting of phenyl and pyridinyl, and the substituents for R^2 are selected from the group consisting of halogen, up to per-halosubstitution and Y_n , wherein $n = 0-3$, and each Y is independently selected from the group consisting of substituted and unsubstituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, $-NO_2$, $-NH_2$, $-C(O)-C_{1-6}$ alkyl, $-C(O)N-(C_{1-6}$ alkyl) $_2$, $-C(O)NH-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl, $-NHC(O)H$, $-NHC(O)OH$, $-N(C_{1-6}$ alkyl) $C(O)-C_{1-6}$ alkyl, $-N-(C_{1-6}$ alkyl) $C(O)-C_{1-6}$ alkyl, $-NHC(O)-C_{1-6}$ alkyl, $-OC(O)NH C_{6-14}$ aryl, $-NHC(O)O-C_{1-6}$ alkyl, $-S(O)-C_{1-6}$ alkyl and $-SO_2-C_{1-6}$ alkyl,

wherein if Y is a substituted group, it is substituted by one or more halogen, up to per-halosubstitution.

3. A method as in claim 1, wherein B is up to a tricyclic aromatic ring structure selected from the group consisting of



which is substituted or unsubstituted by halogen, up to per-halosubstitution, and
5 wherein

$n = 0-3$ and

each X is independently selected from the group consisting of $-CN$, $-CO_2R^5$,
 $-C(O)NR^5R^5'$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^5'$, $-NR^5C(O)OR^5'$, $-NR^5C(O)R^5'$,
10 C_1-C_{10} alkyl, C_{2-10} -alkenyl, C_{1-10} -alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24}
alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alk heteroaryl, and substituted C_1-C_{10} alkyl,
substituted C_{2-10} -alkenyl, substituted C_{1-10} -alkoxy, substituted C_3-C_{10} cycloalkyl,
substituted C_4-C_{23} alk heteroaryl and $-Y-Ar$;

wherein if X is a substituted group, it is substituted by one or more
substituents independently selected from the group consisting of $-CN$, $-CO_2R^5$,
15 $-C(O)R^5$, $-C(O)NR^5R^5'$, $-OR^5$, $-SR^5$, $-NR^5R^5'$, $-NO_2$, $-NR^5C(O)R^5'$, $-NR^5C(O)OR^5'$ and
halogen up to per-halosubstitution;

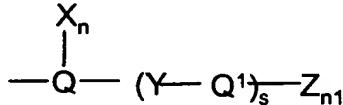
wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_{2-10} -
alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23}
alk heteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_{2-10} -

alkenyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₆-C₁₄ aryl and up to per-halosubstituted C₃-C₁₃ heteroaryl,

wherein Y is -O-, -S-, -N(R⁵)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -NR⁵C(O)NR⁵'-, -NR⁵C(O)-, -C(O)NR⁵'-, -(CH₂)_mS-, -(CH₂)_mN(R⁵)-, -O(CH₂)_m-, 5 -CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁵)(CH₂)_m-,
m = 1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 10 3 and each Z is independently selected from the group consisting of -CN, -C(O)R⁵, -CO₂R⁵, -C(O)NR⁵R⁵', -C(O)R⁵', -NO₂, -OR⁵, -SR⁵, -NR⁵R⁵', -NR⁵C(O)OR⁵', -NR⁵C(O)R⁵', C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl, C₇-C₂₄ alkaryl, C₄-C₂₃ alkheteroaryl, substituted C₁-C₁₀ alkyl, substituted C₃-C₁₀ cycloalkyl, substituted C₇-C₂₄ alkaryl and substituted C₄-C₂₃ alkheteroaryl; wherein if Z is a 15 substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, -CO₂R⁵, -C(O)NR⁵R⁵', -OR⁵, -SR⁵, -NO₂, -NR⁵R⁵', -NR⁵C(O)R⁵' and -NR⁵C(O)OR⁵'.

4. A method of claim 1, wherein B is



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wherein

Y is selected from the group consisting of -O-, -S-, -CH₂-, -SCH₂-, -CH₂S-, -CH(OH)-, -C(O)-, -CX^a₂, -CX^aH-, -CH₂O- and -OCH₂-,

25 X^a is halogen,

Q is a six member aromatic structure containing 0-2 nitrogen, substituted or unsubstituted by halogen, up to per-halosubstitution;

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~~Q¹ is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or unsubstituted by halogen up to per-halosubstitution,~~

~~s = 0 or 1, and~~

5 ~~X, Z, n and n1 are as defined in claim 1.~~

5. A method as in claim 4, wherein

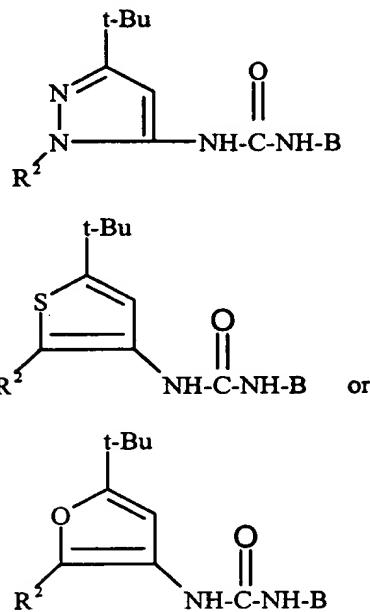
~~Q is phenyl or pyridinyl, substituted or unsubstituted by halogen, up to per-halosubstitution,~~

10 ~~Q¹ is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, or Y-Q¹ is phthalimidinyl substituted or unsubstituted by halogen up to per-halo substitution, and~~

15 ~~Z and X are independently selected from the group consisting of -R⁶, -OR⁶ and -NHR⁷, wherein R⁶ is hydrogen, C₁-C₁₀-alkyl or C₃-C₁₀-cycloalkyl and R⁷ is selected from the group consisting of hydrogen, C₃-C₁₀-alkyl, C₃-C₆-cycloalkyl and C₆-C₁₀-aryl, wherein R⁶ and R⁷ can be substituted by halogen or up to per-halosubstitution.~~

6. A method as in claim 4, wherein Q is phenyl, Q¹ is phenyl or pyridinyl, Y is -O-, -S- or -CH₂-, and X and Z are independently Cl, F, CF₃, NO₂ or CN.

7. A method as in claim 1, which comprises administering a compound of one of the formulae or a pharmaceutically acceptable salt thereof:



wherein B and R² are as defined in claim 1.

8. A method as in claim 7, wherein R² is selected from substituted and unsubstituted members of the group consisting of phenyl and pyridinyl, wherein if R² is a substituted group, it is substituted by one or more substituents selected from the group consisting of halogen and W_n, wherein n = 0-3, and W is selected from the group consisting of -NO₂, -C₁₋₃ alkyl, -NH(O)CH₃, -CF₃, -OCH₃, -F, -Cl, -NH₂, -OC(O)NH up to per-halosubstituted phenyl, -SO₂CH₃, pyridinyl, phenyl, up to per-halosubstituted phenyl and C₁-C₆ alkyl substituted phenyl.

9. A method as in claim 1, comprising administering an amount of compound of formula I effective to inhibit p38.

10. A method as in claim 1, wherein the compound of formula I displays p38 activity (IC₅₀) better than 10μM as determined by an in-vitro kinase assay.

11. A method according to claim 1, wherein the disease is mediated by a cytokine or protease regulated by p38.

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12. A method according to claim 1, wherein R² is t-butyl.

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13. A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit p38.

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14. A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit production of a disease-mediating cytokine or protease.

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15. A method according to claim 1, wherein the disease is an inflammatory or immunomodulatory disease.

16. A method according to claim 1, wherein the disease is rheumatoid arthritis, osteoarthritis, osteoporosis, asthma, septic shock, inflammatory bowel disease, or the result of host-versus-graft reactions.

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